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(54) HALOALKYL HETEROARYL BENZAMIDE COMPOUNDS

HALOALKYL-HETEROARYL-BENZAMID-VERBINDUNGEN

COMPOSÉS HALOALKYL HÉTÉROARYL BENZAMIDE

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Description

FIELD OF THE INVENTION

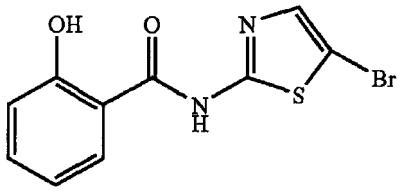
[0001] The present invention is directed to new heterocyclic compounds, pharmaceutically acceptable salts thereof, compositions comprising such compounds and salts, and use of those compounds, salts, and compositions for the treatment of viral disease. It is also concerned with inhibition of viral pathogen activity in humans and animals. It is also concerned with treatment of hepatitis C virus (HCV), hepatitis B virus (HBV), and related viral pathogen infection in humans and animals.

BACKGROUND

[0002] The present application relates generally to the field of thiazolide compounds. In particular, the application relates to haloalkyl-substituted thiazolide compounds.

[0003] Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) are major public health problems, causing more than an estimated 500 million chronic infections worldwide. Both viruses cause significant progressive liver disease and are major risk factors for primary hepatocellular carcinoma. Current standards of care for both HBV and HCV infections, while effective in many cases, are sub-optimal and fail to produce either a virologic or a clinical 'cure' in most. The development of drug-resistance in HBV, including strains carrying resistance to multiple currently used agents, is an emerging clinical problem, and drug-resistance for future HCV therapies is predicted to be a significant clinical issue.

[0004] US 2007/0167504 discloses methods for treating viral hepatitis. The following compound is disclosed:

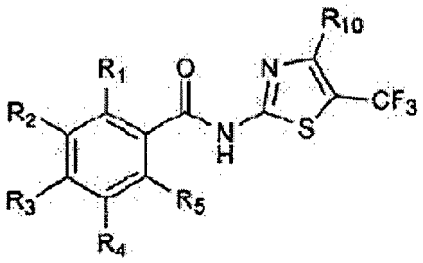


RM-4832

SUMMARY

[0005] This invention provides novel compounds and pharmaceutical compositions that treat viral pathogens, as well as methods of synthesizing and using the compounds to treat and inhibit viral infection. The compounds of this invention are haloalkyl heteroaryl benzamides as defined in claim 1.

[0006] In one embodiment, this invention provides a compound of Formula II:



(II)

wherein:

R_1 is hydroxy or C_1-C_3 alkanoyloxy; and

R_2 through R_5, and R_{10} are H,

or a pharmaceutically acceptable salt thereof.

[0007] These compounds are useful in treating disorders and conditions caused by viral pathogens.

[0008] In another embodiment, this invention provides or contemplates a composition comprising a compound of formula II and a carrier.

[0009] In another embodiment, this invention provides or contemplates a pharmaceutical composition comprising a compound of Formula II and a pharmaceutically acceptable carrier.

[0010] In another embodiment, this invention provides or contemplates a method of treatment of viral infection comprising administering to a human or animal afflicted with viral infection a therapeutically effective amount of a compound of Formula II.

[0011] In a more specific embodiment, this invention provides or contemplates a method of treatment of HCV infection comprising administering to a human or animal afflicted with viral infection a therapeutically effective amount of a compound of Formula II.

[0012] In a more specific embodiment, this invention provides or contemplates a method of treatment of HBV infection comprising administering to a human or animal afflicted with viral infection a therapeutically effective amount of a compound of Formula II.

[0013] In other embodiments, the present invention provides or contemplates methods for inhibiting or modulating a viral pathogen. In other embodiments, the present invention provides or contemplates methods for treating a viral-mediated disorder in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of a compound or composition of compounds of this invention. In other embodiments, this invention provides or contemplates methods for treating HCV, HBV, and other viral infections comprising administering pharmaceutical compositions of the invention to a patient in need thereof. For example, the patient may have a chronic HCV infection. The present invention also contemplates the use of compounds disclosed herein for use in the manufacture of a medicament for the treatment of a disease or condition ameliorated by the inhibition or modulation of viral activity.

DETAILED DESCRIPTION

[0014] Unless otherwise specified, "a" or "an" means "one or more."

[0015] In one embodiment, this invention provides or contemplates a compound of Formula II as defined above.

[0016] In a more specific embodiment, this invention provides or contemplates a compound of Formula II wherein R_1 is hydroxy or acetoxy.

[0017] In another more specific embodiment, this invention provides or contemplates a compound of Formula II wherein the compound is 2-hydroxy-N-(5-(trifluoromethyl)thiazol-2-yl)benzamide.

[0018] In another embodiment this invention provides or contemplates pharmaceutical compositions comprising one or more compounds of the present invention together with a pharmaceutically acceptable carrier (*e.g.*, a diluent or excipient). It other embodiments this invention provides or contemplates methods of making and using the compounds and compositions. In more specific embodiments, the invention provides or contemplates pharmaceutical compositions which comprise therapeutically effective amounts of the compound of this invention and methods of using such compositions for treating HCV, HBV, and other viral infections.

[0019] Because compounds of this invention may be used in the diagnosis as well as the treatment of disease, isotopically labeled versions of these compounds are included in this disclosure and in the claims. All references to elements in compounds of this invention are intended to include all isotopes of those elements, including unstable isotopes. For example, references to "hydrogen" or H in formulas or in claims are intended to include deuterium, (D) and tritium (T.)

[0020] In another embodiment, this invention provides or contemplates a kit, comprising, in a compartment, at least one pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, an effective amount of at least one compound of the invention. In some embodiments, the kit further comprises written instructions for administering the pharmaceutical composition. In some embodiments, written instructions for administering concern indications noted elsewhere in this disclosure. In some embodiments, written instructions for administering concern an administration regimen noted elsewhere in this disclosure.

[0021] As used in the present specification the following terms have the meanings indicated:

[0022] The term "salts" is used in its broadest sense. For example, the term salts includes hydrogen salts and hydroxide salts with ions of the present compound. In some embodiments, the term salt may be a subclass referred to as pharmaceutically acceptable salts, which are salts of the present compounds having a pharmacological activity and which are neither biologically nor otherwise undesirable. In all embodiments, the salts can be formed with acids, such as, without limitation, hydrogen, acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycero-phosphate, hemisulfate, heptanoate, hexanoate, hydrochloride hydrobromide, hydroiodide, 2-hydroxyethane-sulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, thiocyanate, tosylate and undecanoate. In all embodiments, the salts can be formed with bases, such as, without limitation, hydroxide, ammonium salts, alkali metal salts such as lithium, sodium and potassium salts, alkaline earth metal salts such as

calcium, magnesium salts, aluminum salts, salts with organic bases such as ammonia, methylamine, diethylamine, ethanolamine, dicyclohexylamine, N-methylmorpholine, N-methyl-D-glucamine, and salts with amino acids such as arginine and lysine. Basic nitrogen-containing groups can be quarternized with agents including lower alkyl halides such as methyl, ethyl, propyl and butyl chlorides, bromides and iodides; dialkyl sulfates such as dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides such as benzyl and phenethyl bromides.

[0023] The terms "therapeutically acceptable salt," and "pharmaceutically acceptable salt," as used herein, represent salts or zwitterionic forms of the compounds of the present invention which are water or oil-soluble or dispersible; which are suitable for treatment of diseases without undue toxicity, irritation, and allergic-response; which are commensurate with a reasonable benefit/risk ratio; and which are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds of the present invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present invention contemplates sodium, potassium, magnesium, and calcium salts of the compounds of the compounds of the present invention and the like.

[0024] Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy, phenol or similar group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[0025] The term "carrier" is used in its broadest sense. For example, the term carrier refers to any carriers, diluents, excipients, wetting agents, buffering agents, suspending agents, lubricating agents, adjuvants, vehicles, delivery systems, emulsifiers, disintegrants, absorbents, preservatives, surfactants, colorants, flavorants, and sweeteners. In some embodiments, the carrier may be a pharmaceutically acceptable carrier, a term narrower than carrier, because the term pharmaceutically acceptable carrier" means a non-toxic that would be suitable for use in a pharmaceutical composition.

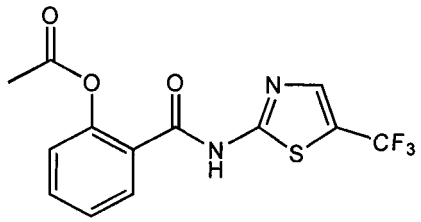
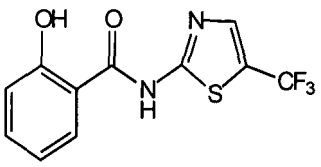
[0026] The present invention also relates to a pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, an effective amount of at least one compound of the invention.

[0027] The term effective amount is used in its broadest sense. The term, for example, refers to the amount required to produce a desired effect.

[0028] In some embodiments, the compound of the invention is present in a pharmaceutical composition in an effective amount for treating HCV infection (e.g., chronic HCV infection). "Treating HCV infection" may refers to: (i) preventing HCV infection from occurring in an animal that may be predisposed to HCV infection but has not yet been diagnosed as having it; (ii) inhibiting or slowing HCV infection, e.g. arresting its development; (iii) relieving chronic infection, e.g. causing its regression; (iv) improving a symptom in a subject having chronic infection; and/or (v) prolonging the survival of a subject having chronic infection.

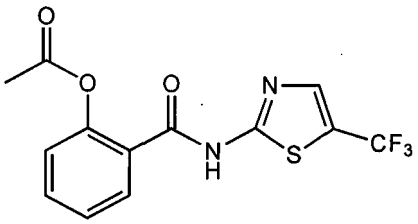
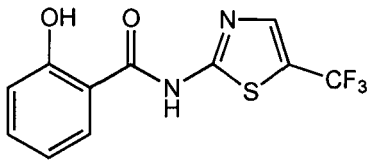
[0029] Examples of compounds of the present invention may include, but are not limited to the following compounds listed in Table 1 below:

TABLE 1

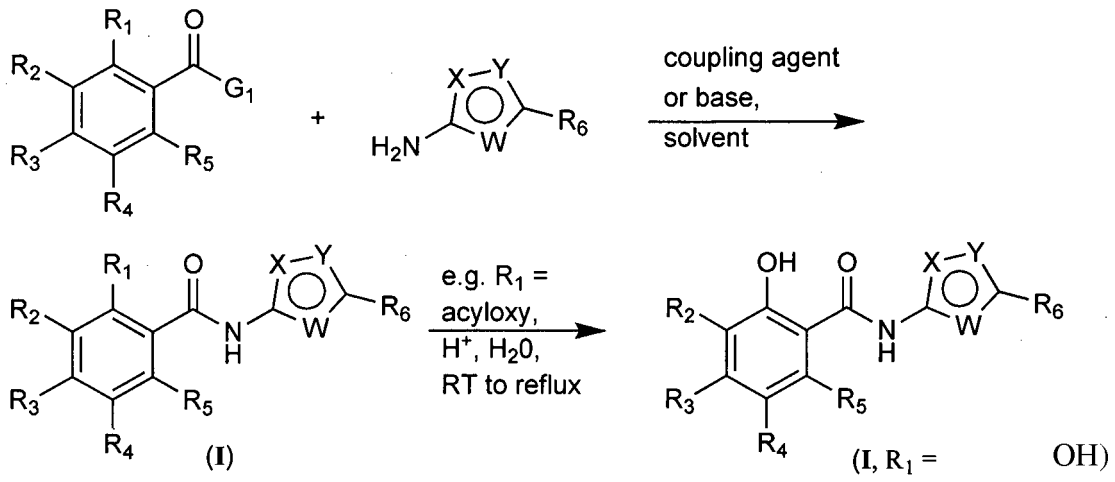
No.	Structure
1	
2	

[0030] Table 2 designates the melting points of various compounds.

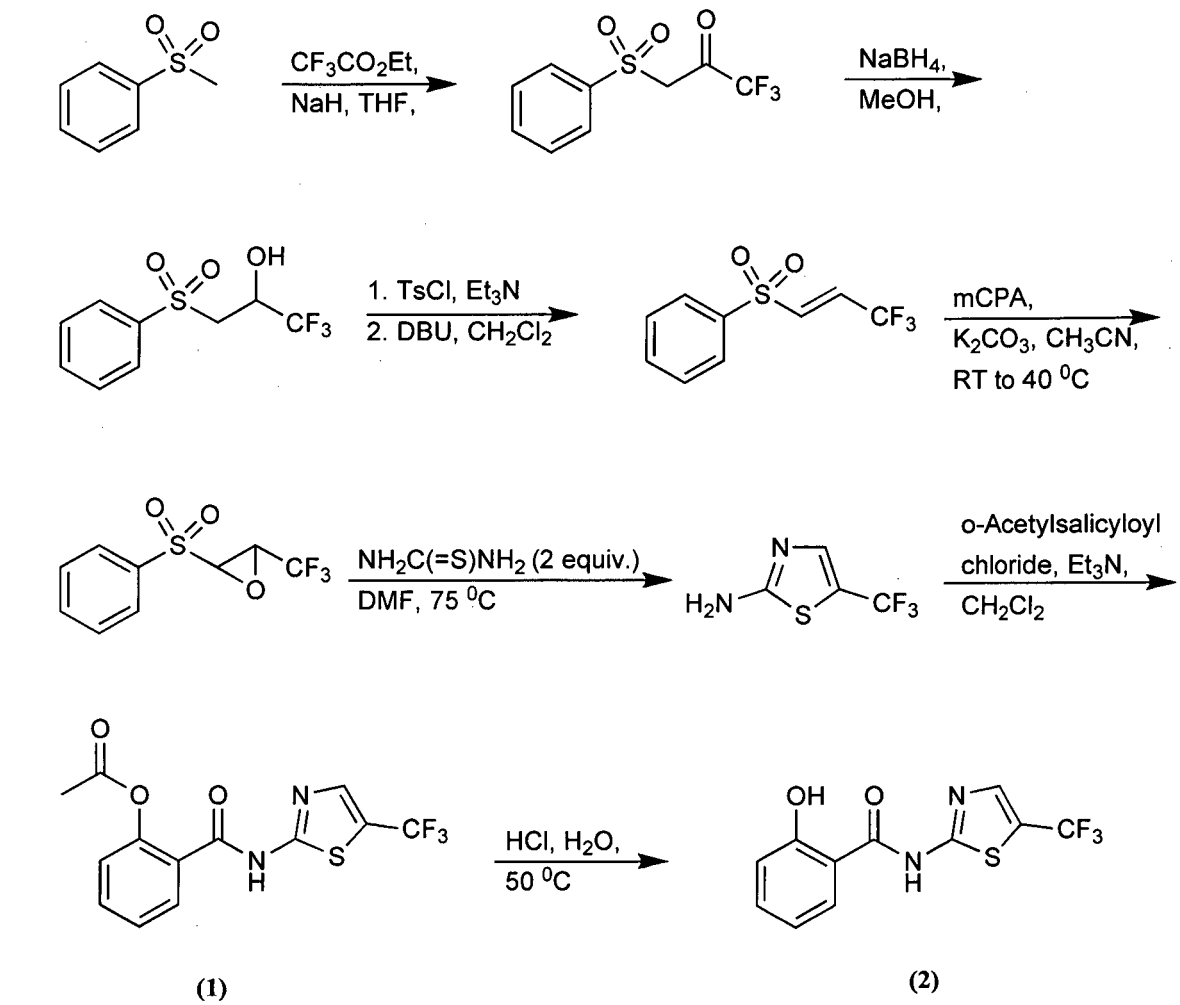
TABLE 2

No.	Structure	Melting Point (°C)
1		127.5-129.0
2		260-264 (dec)

[0031] Compounds of Formula (II) may be synthesized by reacting an aroyl derivative, wherein G_1 is hydroxy, chloro, fluoro, bromo, alkoxy and the like with a heteroaromatic amine as shown below, wherein W is S, X is N, Y is C, R6 is CF_3 and R2-R5 are H, under suitable reaction conditions. In some embodiments, the reaction may be generically represented as follows:



[0032] Examples of the invention, compounds (1) and (2), may be synthesized by the method described in the following reaction scheme. 2-Amino-5-trifluoromethyl-thiazole was prepared by a modification of the procedure of Laduron et al. J. Fluorine Chem. 1995, 73, 83-86. Coupling of o-acetylsalicyloyl choride and 2-Amino-5-trifluoromethylthiazole in the presence of a suitable base, including tertiary amines like triethylamine, in a suitable inert solvent like dichloromethane, at about 0 °C to about ambient room temperature, affords compound (1). Hydrolysis of the acetyl moiety of compound (1) with dilute hydrochoric acid at room temperature to about 50 °C yields compound (2).



[0033] The compositions of the present invention may be formulated as solid or liquid dosage forms, or as pastes or

ointments, and may optionally contain further active ingredients.

[0034] A pharmaceutical composition of the present invention comprises a pharmaceutically acceptable carrier, which is not particularly limited, and includes a wide range of carriers known to those of ordinary skill in the art, and including wetting or dispersing agents, starch derivatives, excipients, and the like. Tablet embodiments may optionally comprise a coating of a substance that constitutes an enteric coating, i.e., a coating that substantially insoluble in gastric secretion but substantially soluble in intestinal fluids.

[0035] Pharmaceutical compositions comprising the compounds of the present invention are in some embodiments formulated for oral administration and are optionally in the form of a liquid, for example an emulsion or a solution or a suspension in water or oil such as arachis oil, or other liquid. Formulations of non-aqueous micellar solutions may be prepared according to the method disclosed in U.S. Patent 5,169,846. Alternatively, tablets can be manufactured, for example, by performing the following steps: wet granulation; drying; and compression. Film coating may generally be performed with organic solvents.

[0036] The compounds of the present invention can be used in a method, comprising administering to a subject at least one compound of the present invention in an amount in an effective amount for treating HCV infection (e.g., chronic HCV infection). In some embodiments, the method, comprising administering to a subject at least one pharmaceutical composition which comprises at least one compound of the present invention in an amount in an effective amount for treating HCV infection (*e.g.*, chronic HCV infection).

[0037] In some embodiments, the subject is chosen from animals. In some embodiments, the subject is chosen from mammals. In some embodiments, the subject is chosen from pets, such as mice, dogs, cats, etc. In some embodiments, the subject is chosen from humans.

[0038] In some embodiments, the invention provides a method of treating a viral infection in a subject, comprising administering to the subject at least one dose of an effective amount of at least one compound of the present invention. In some embodiments, the invention provides a method of treating a viral infection in a subject, comprising administering to the subject at least one dose of an effective amount of at least one pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, at least one compound of the present invention.

[0039] In some embodiments the antiviral treatment or prophylactic dosages of the compound of the present invention may depend upon the weight of the subject, and may be inferred by one of ordinary skill without undue experimentation by reference to the following examples, which are set forth for purposes of illustration and are not intended to be limiting.

[0040] The inventive compounds and compositions may be administered locally or systemically by any means known to an ordinarily skilled artisan. For example, the inventive compounds and compositions may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intraarterial, intramuscular, intraperitoneal, intrathecal, intraventricular, intrasternal, intracranial or intraosseous injection and infusion techniques. The exact administration protocol will vary depending upon various factors including the age, body weight, general health, sex and diet of the patient; the determination of specific administration procedures would be routine to an ordinarily skilled artisan.

[0041] Dose levels on the order of about 0.1 to about 100 mg/kg of the active ingredient compound are useful in the treatment of the above conditions (*e.g.*, 0.1 mg/kg-day). In some embodiments, the amounts range from about 1 to about 10 mg/kg, and in other embodiments, the amounts range from about 2 to about 5 mg/kg. The specific dose level for any particular patient will vary depending upon a variety of factors, including the activity and the possible toxicity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the rate of excretion; drug combination; the severity of the particular disease being treated; and the form of administration. Typically, in vitro dosage-effect results provide useful guidance on the proper doses for patient administration. Studies in animal models are also helpful. The considerations for determining the proper dose levels are well known in the art.

[0042] Any administration regimen for regulating the timing and sequence of drug delivery can be used and repeated as necessary to effect treatment. Such regimen may include multiple uses or preadministration and/or co-administration and/or postadministration with food, liquid, or water.

[0043] As noted above, this invention provides or contemplates a kit, comprising at least one compound of the invention. The kit could take any form. By way of example, a kit includes one or more containers for storing a pharmaceutical composition. In some embodiments, a container contains written instructions for administering the pharmaceutical composition. In some embodiments, a container contains is the substrate for the written instructions for administering the pharmaceutical composition. In some embodiments, the written instructions for administering the pharmaceutical composition are affixed to a container, for example, as in a container for filling a prescription sometimes has written instructions affixed on a surface.

EXAMPLES

1. Materials and Methods.

1.1 Materials.

[0044] All test compounds were provided by Romark Laboratories, Nitazoxanide and Tizoxanide were used as standards.

1.2. HBV studies.

1.2.1. Antiviral assays.

[0045] HBV antiviral assays were conducted as previous described [Korba and Gerin, Antiviral Res. 19:55 (1992Confluent cultures of 2.2.15 cells were maintained on 96-well flat-bottomed tissue culture plates (confluence in this culture system is required for active, high levels of HBV replication equivalent to that observed in chronically-infected individuals [Sells et al.. J. Virol. 62, 2836-2844 (1988); Korba and Gerin (1992)]. Cultures were treated with nine consecutive daily doses of the test compounds. HBV DNA levels were assessed by quantitative blot hybridization 24 hr. after the last treatment. Cytotoxicity was assessed by uptake of neutral red dye 24 hr. following the last treatment.

1.2.3. Production of HBV proteins.

[0046] Cultures of 2.2.15 cells were treated under standard procedures and semiquantitative EIA-based analysis of HBV proteins was performed as previously described [Korba and Gerin, Antivir. Res. 28, 225-242 (1995)], except that HBeAg was analyzed ETI-EBK Plus®(DiaSorin, Inc., Stillwater, MN USA). Samples were diluted (2 to 10-fold) to bring levels into the dynamic response ranges of the EIA's. HBsAg, and HBeAg were analyzed from culture medium samples and HBcAg was analyzed from intracellular lysates. Intracellular HBV RNA was assessed by quantitative northern blot hybridization (Korba and Gerin, 1995).

1.3. HCV studies.

[0047] Antiviral activity of test compounds was assessed in a 3-day assay using the stably-expressing HCV replicon cell line, AVA5 (sub-genomic CON1, genotype 1b) [Blight et al., Science 290, 1972-1974 (2000)] maintained as sub-confluent cultures on 96-well plates as previously described (Okuse et al., Antiviral Research 65, 23-34 (2005)]. Antiviral activity was determined by blot hybridization analysis of intracellular HCV RNA (normalized to the level of cellular B-actin RNA in each culture sample) and cytotoxicity was assessed by neutral red dye uptake after 3 days of treatment. Additional studies were performed using Huh7 cells containing another HCV replicon, H/FL-Neo, a genotype Ia full length construct [Blight et al., J. Virol. 77, 3181-3190 (2003)]. For studies involving human serum, standard culture medium (which contains 10% fetal bovine serum) and assay conditions were maintained.

1.4. Presentation of results.

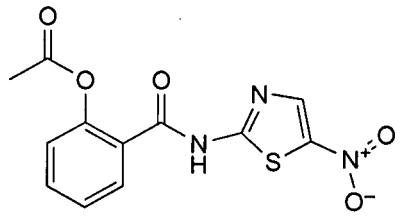
[0048] EC_{50}, EC_{90} and CC_{50} values (± standard deviations [S.D.]) were calculated by linear regression analysis using data combined from all treated cultures (Korba and Gerin, 1992; Okuse et al., 2005). EC_{50} and EC_{90} are drug concentrations at which a 2-fold, or a 10-fold depression of intracellular HBV DNA or HCV RNA (relative to the average levels in untreated cultures), respectively, was observed. CC_{50} is the drug concentration at which a 2-fold lower level of neutral red dye uptake (relative to the average levels in untreated cultures) was observed. Selectivity index (S.I.) was calculated as CC_{50}/EC_{90} for HBV assays and CC_{50}/EC_{50} for HCV assays. EC_{90} values were used for calculation of the S.I. in HBV assays since at least a 3-fold depression of HBV DNA levels is typically required to achieve statistical significance in this assay system (Korba and Gerin, 1992). For combination treatments, EC_{50}, EC_{90}, CC_{50} and S.I. are presented for the first compound listed. The molar ratio of the compounds in each combination is also indicated.

2. Results

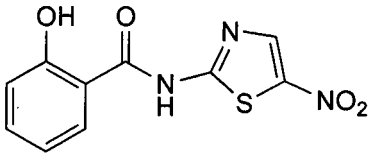
[0049]

TABLE 3. HBV Extracellular Virion Assay Results.

Compd #		CC_{50} (μM)		EC_{50} (VIR) (μM)		EC_{90} (VIR) (μM)		SI (VIR)
Nitazoxanide (reference)	>	100.0		A		c	>	121
Tizoxanide (reference)	>	100.0		A		C	>	172
1	>	100.0		D	D E >	E	>	11
2	>	100.0		D	D E >	E	>	11
Legend: A: 0.05-0.2; B: 0.2-0.8; C: 0.8-3.2; D: 3.2-4.0; E: >4.0								



Nitazoxanide (reference)



Tizoxanide (reference)

Table 4 presents data from the primary HCV replicon cell assay.

TABLE 4. Primary HCV Replicon Cell Assay.

	PRIMARY ASSAY, GENOTYPE 1B			
Compound	CC50 (μM)	EC50 (μM)	EC90 (μM)	SI
Nitazoxanide (reference)	32.0	B	C	169.0
Tizoxanide (reference)	15.0	B	C	100.0
1	3.7	D	E	0.9
2	0.46	A	A	58.0
EC50 & EC90 Legend A: 0.005-0.05; B: 0.05-0.5; C: 0.5-1.0; D: 1.0 - 5.0; E: > 5.0				

TABLE 5. Antiviral Activity of Thiazolides Against Paramyxovirus, Influenza A and Coronavirus in Cell Assays

		Paramyxovirus (Sendai virus)-37RC cells				Influenza A (PR8)- MDCK cells				Coronavirus (CCoV)- A72 cells			
		Virus Yield		Toxicity	S.I.	Virus Yield		Toxicity	S.I.	Virus Yield		Toxicity	S.I.
		ID_{50}	ID_{90}	LD_{50} (MTT)	LD_{50} /ID_{50}	ID_{50}	ID_{90}	LD_{50} (MTT)	LD_{50} /ID_{50}	ID_{50}	ID_{90}	LD_{50} (MTT)	LD_{50} /ID_{50}
Compound	RM#	μg/ml	μg/ml	μg/ml		μg/ml	μg/ml	μg/ml		μg/ml	μg/ml	μg/ml	
Nitazoxanide (reference)	NTZ	1	6	>50	>50	1	7	>50	>50				
Tizoxanide (reference)	TIZ	0.5	5	>50	>100	1	9	>50	>50	1	1.5	>50	>50
1	RM5036												
2	RM5037												

TABLE 6. Antiviral Activity of Thiazolides Against Rhinovirus, Respiratory Syncytial Virus and Herpesvirus in Cell Assays

		Rhinovinis(RHV-2) HeLa R19 cells				Respiratory Syncytial Virus (RV-A2)-HeLa cells					Herpesvirus (HSV-1) - Hep-2 cells		
		Virus Yield		Toxicity	S.I.	Virus Yield		Toxicity		S.I.	Virus Yield	Toxicity	S.I.
		ID_{50}	ID_{90}	LD_{50} (MTT)	LD_{50}/ID_{50}	ID_{50}	ID_{90}	LD_{50} (MTT)	LD_{50}/ID_{50}	ID_{50}	ID_{90}	LD_{50} (MTT)	LD_{50}/ID_{50}
Compound	RM#	µg/ml	µg/ml	µg/ml		µg/ml	µg/ml	µg/ml		µg/ml	µg/ml	µg/ml	
Nitazoxanide (reference)	NTZ	2.5	>50	>50	>20					0.025	0.5	>50	>2000
Tizoxanide (reference)	TIZ	0.3	40	>50	>167	0.5	-	3	6	2	5	50	25
1	RM5036	9	>50	>50	>5.5					0.2	2	>50	>250
2	RM5037												

TABLE 7. Antiviral Activity of Thiazolides Against Rotavirus (2 strains) and Adenovirus in Cell Assays

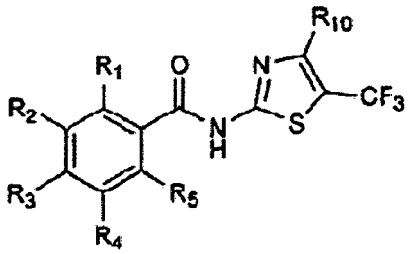
		Rotavirus (Simian SA11)-MA104 cells				Rotavirus (WAG8P1) - MA104 cells				Adenovirus (Ad5)- HeLa R19 cells			
		Virus Yield		Toxicity	S.I.	Virus Yield		Toxicity	S.I.	Virus Yield		Toxicity	S.I.
		ID_{50}	ID_{90}	LD_{50} (MTT)	LD_{50}/ID_{50}	ID_{50}	ID_{90}	LD_{50} (MTT)	LD_{50}/ID_{50}	ID_{50}	ID_{90}	LD_{50} (MTT)	LD_{50}/ID_{50}
Compound	RM#	µg/ml	µg/ml	µg/ml		µg/ml	µg/ml	µg/ml		µg/ml	µg/ml	µg/ml	
Nitazoxanide (reference)	NTZ	1	10	>50	>50	10	40	>50	>5	1.5	15	>50	>33.3
Tizoxanide (reference)	TIZ	0.5	4	>50	>100	1	15	>50	>50	0.2	0.3	0.8	5
1	RM5036									0.1	3.5	4	40
2	RM5037												

TABLE 8. Antiviral Activity of thiazolides Against Rhabdovirus in Cell Assays

		Rhabdovirus (VSV) - MA104 cells			
		Virus Yield		Toxicity	S.I.
		ID_{50}	ID_{90}	LD_{50} (MTT)	LD_{50} /ID_{50}
Compound	RM#	μg/ml	μg/ml	μg/ml	
Nitazoxanide (reference)	NTZ				
Tizoxanide (reference)	TIZ	2	15	50	25
1	RM5036				
2	RM5037				

Claims

1. A compound of Formula II:



(II)

wherein:

R_1 is hydroxy or C_1-C_3 alkanoyloxy; and
R_2 through R_5, and R_{10} are H,

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein R_1 is hydroxy or acetoxy.

3. The compound of claim 1 or 2, wherein the compound is 2-hydroxy-N-(5-(trifluoromethyl)thiazol-2-yl)benzamide.

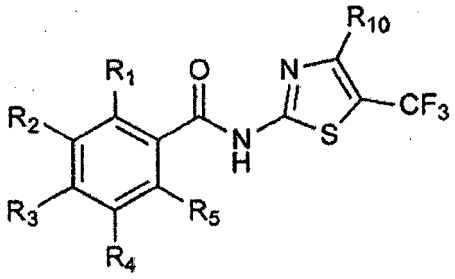
4. The compound of any of claims 1-3 for use in a method for treating a viral infection.

5. The compound for use according to claim 4 wherein the viral infection is Hepatitis C Virus.

6. The compound for use according to claim 4 wherein the viral infection is Hepatitis B Virus.

Patentansprüche

1. Verbindung der Formel (II):



(II)

worin:

R_1 Hydroxy oder C_{1-3}-Alkanoyloxy ist; und
R_2 bis R_5 und R_{10} H sind,

oder ein pharmazeutisch annehmbares Salz davon.

2. Verbindung gemäss Anspruch 1, worin R_1 Hydroxy oder Acetoxy ist.

3. Verbindung gemäss Anspruch 1 oder 2, wobei die Verbindung 2-Hydroxy-N-(5-(trifluormethyl)thiazol-2-yl)benzamid ist.

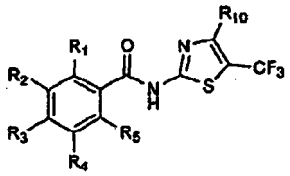
4. Verbindung gemäss einem der Ansprüche 1 bis 3 zur Verwendung in einem Verfahren zur Behandlung einer Virusinfektion.

5. Verbindung zur Verwendung gemäss Anspruch 4, wobei die Virusinfektion ein Hepatitis C-Virus ist.

6. Verbindung zur Verwendung gemäss Anspruch 4, wobei die Virusinfektion ein Hepatitis B-Virus ist.

Revendications

1. Composé de formule II :



(II)

dans laquelle :

R_1 est hydroxy ou alcanoyloxy en C_1-C_3 ; et
R_2 à R_5, et R_{10} sont H,

ou un sel pharmaceutiquement acceptable de celui-ci.

2. Composé selon la revendication 1, dans lequel R_1 est hydroxy ou acétoxy.

3. Composé selon la revendication 1 ou 2, dans lequel le composé est le 2-hydroxy-N-(5-(trifluorométhyl)thiazol-2-yl)benzamide.

4. Composé selon l'une quelconque des revendications 1 à 3 pour une utilisation dans un procédé de traitement d'une infection virale.

5. Composé pour une utilisation selon la revendication 4, dans lequel l'infection virale est le virus de l'hépatite C.

6. Composé pour une utilisation selon la revendication 4, dans lequel l'infection virale est le virus de l'hépatite B.

REFERENCES CITED IN THE DESCRIPTION

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